ATTACHMENT A

Remarks

Claims 1, 3, 4, 6, 7, 9, 10, 14, 15, 20-22, 24, 25, 27, 29-35 stand pending in the present application. By this Amendment, Applicants have amended claims 3, 4, 9, 10, 14, 15, 20, 21, 24, 25 and 29 and canceled claims 23, 26 and 28. Applicants respectfully submit that the present application is in condition for allowance based on the discussion which follows.

The Examiner noted that the Declaration was not in compliance with 37 C.F.R. § 1.67(a) for failing to identify the citizenship of each inventor. By this Amendment, Applicants have submitted a new Declaration for inventor Quach identifying his citizenship as being French, in compliance with 37 C.F.R. § 1.67(a).

The Examiner continues to allege that the specification as filed fails to provide sufficient subject matter for SEQ ID No. 8. The Examiner correctly notes that SEQ ID No. 8 indicates that the amino acid at position 56 is lysine. However, the Examiner alleges that there is inadequate antecedent basis in the originally filed specification to support the "correction" to SEQ ID No. 8 alleging that the amino acid sequence at positions 56 of the original application was not lysine. Further, the Examiner alleges that while the specification teaches that the amino acid at position 56 of the amino acid sequence of ULIP-4 is almost certainly lysine, the Examiner alleges that the specification as filed is not deemed sufficient to support the correction of SEQ ID No. 8.

Contrary to the Examiner's allegation, the specification as filed does fully support the correction in SEQ ID No. 8 amino acid at position 56 from histidine to lysine. Specifically, one of ordinary skill in the art would readily appreciate that the specification

as filed does support the correction of the amino acid at position 56. First, on page 18 as filed, the specification notes that the stop codon at position 56 is almost certainly lysine. Further support of Applicants' assertion is provided in Attachment A to this Amendment where Applicants have submitted an amino acid sequence of human ULIP-4 deposited in Genbank under accession number NP-006417. Applicants note that the amino acid in position 56 of the Genbank sequences is lysine as is taught by the specification of the present application. Therefore, Applicants repeat their assertion that the correction entered in SEQ ID No. 8, position 56 from histidine to lysine, does not constitute new matter.

Claims 3, 4, 23, 24 and 28 were objected to. By this Amendment, Applicants have amended claims 3, 4, and canceled claims 23 and 28 thereby obviating their objection to the claims.

Claim 10 was rejected under 35 U.S.C. § 101 for failing to include steps in the recited claim. By this Amendment, claim 10 has been amended to include steps thereby obviating the rejection to claim 10 under 35 U.S.C. § 101.

Claims 3, 6, 7, 9, 10, 14, 15 and 20-29 were rejected under 35 U.S.C. § 112, first paragraph for containing subject matter not described in the specification in a way as to enable one of ordinary skill in the art to practice the claimed invention.

The Examiner reiterates the rejection to the specification alleging that Figure 12 and SEQ ID No. 8 do not depict the same amino acid sequences as Figure 12 includes an asterisk at position 56 representing a "stop codon" whereas SEQ ID No. 8 indicates that lysine occurs at position 56 within the sequence. By this Amendment, Applicants have amended the sequence listing of the specification to include two additional SEQ ID

numbers, namely SEQ ID Nos. 9 and 10 which correspond to amino acids 1-55 and 57-553, respectively, of the sequence shown in Figure 12. In addition, Applicants have amended the specification on page 18 to correct the last sequence number shown in SEQ ID No. 8 and to now describe Figure 12 as representing SEQ ID Nos. 9 and 10 which provide for the inferred amino acid sequence SEQ ID No. 8. Further, Applicants have amended the specification to note that SEQ ID No. 8 is divided into SEQ ID Nos. 9 and 10 which correspond to the amino acids 1-55 and 57-553, respectively.

Furthermore, in Applicants' prior Amendment and in the specification as filed, Applicants have disclosed how they were able to discern that the amino acid at position 56 is lysine. Specifically, the specification as filed on page 18, lines 25-30 notes that a comparison of other ULIP-4 proteins in amino acids which are conserved among species provide the basis for amino acid 56 to be lysine. In addition, as discussed above, by this Amendment, Applicants have submitted Genbank accession number NP-006417 which notes that the amino acid in position 56 is lysine. Therefore, based on the foregoing discussion, Applicants respectfully submit that the specification as filed provides enablement for one of ordinary skill in the art to which it pertains to practice the invention as claimed recognizing that lysine is the amino acid at position 56 of SEQ ID No. 8.

Further, Applicants respectfully submit that the now inclusion of SEQ ID Nos. 9 and 10 which form the basis for the inferred SEQ ID No. 8 fully explain and resolve any alleged inconsistency from the sequence depicted in Figure 12 and SEQ ID No. 8.

With regard to the rejection of claim 10 under 35 U.S.C. § 112, first paragraph, for allegedly not providing enablement for a method of using any fragment of a

polypeptide of SEQ ID No. 8 or a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID No. 7 to detect the presence of anti-CV2 antibodies in any biological sample, Applicants have amended claim 10 to more clearly and succinctly describe Applicants' invention. In particular, claim 10 as amended, recites that the claimed polypeptide fragments bind to anti-CV2 antibodies. Accordingly, one of ordinary skill in the art is enabled to practice the invention as provided in claim 10 (currently amended).

With regard to the rejection of claims 9, 14, 15 and 20-29, the Examiner alleges that the claimed methods for diagnosing a paraneoplastic neurological syndrome and/or the early formation of a tumor would not enable a person skilled in the art to distinguish both conditions and that any tumor would not be characterized by the presence of anti-CV2 antibodies. By this Amendment, claims 9, 14, 15, 25 and 29 have been amended to be directed to a composition, kit or methods "for the diagnosis of paraneoplastic neurological syndromes and the early diagnosis of the formation of tumors in which anti-CV2 antibodies are expressed". Accordingly, the amendment to these claims obviate the rejections to these claims under 35 U.S.C. § 112, first paragraph.

With regard to the rejection of claims 3, 6 and 7, the Examiner alleges that the nucleic acid comprising a sequence coding for the polypeptide of SEQ ID No. 8 would encompass genomic DNA. By this Amendment, claim 3 has been amended to be directed to a cDNA sequence thereby excluding genomic DNA.

Based on the foregoing, Applicants respectfully submit that the claims as pending are enabled and therefore Applicants respectfully request that the rejection to the claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 21 and 25-29 were rejected under 35 U.S.C. § 112, second paragraph. With regard to claims 25-29, the Examiner alleges that the limitation "a tumor of cancerous origin" renders these claims vague and indefinite. By this Amendment, claims 25 and 29 have been amended by removing the term "of cancerous origin" and now recite that the tumor "elicits an auto-immune response in a subject that results in the subject expressing anti-CV2 antibodies". Further by this Amendment, claims 26 and 28 have been canceled. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection to claims 21, 25, 27 and 29 under 35 U.S.C. § 112, second paragraph.

Claims 30-32 were rejected under 35 U.S.C. § 102(b) as being anticipated by Antoine, et al (*Journal of Neurological Sciences* 117:215-223, 1993) (hereinafter "Antoine"). Contrary to the Examiner's allegation, claims 30-32 are not anticipated by Antoine. The subject matter of claims 30-32 are directed to a reagent for use in diagnosis where the reagent includes an antigenic portion of a polypeptide comprising SEQ ID No. 8 in a solid support.

The Examiner alleges that Antoine teaches fixed brain sections that comprise antigenic portions of a polypeptide indigenous to the brain comprising the amino acid sequence set forth in SEQ ID No. 8 to which the anti-CV2 antibodies bind. Contrary to the Examiner's allegation, Antoine merely describes that anti-CV2 antibodies react with 66 kDa proteins. Nowhere does Antoine specifically disclose that the 66 kDa protein is

a polypeptide of SEQ ID No. 8. Therefore, Antoine fails to teach let alone suggest the subject matter of claims 30-32.

Claims 9, 10, 14, 15, 20-24 and 33-35 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Honnorat et al (hereinafter "Honnorat") and Antoine in view of Stefano et al (hereinafter "Stefano"), Okajima et al (hereinafter "Okajima") and U.S. Patents Nos. 5,770,381 and 6,066,475. The Examiner alleges that the prior art establishes a *prima facie* case of obviousness. Further, the Examiner alleges that claims 10 and 30-35 are obvious in view of Hamajima in view of Genbank accession number AB006713.

First, with regard to the rejection of claims 15 and 30-35 as being obvious over Hamajima in view of Genbank accession number AB006713, the Genbank reference discloses the mRNA sequence coding for the human ULIP4 protein. However, this document was published on May 9, 1997, after the priority date of the present application, and thus not prior art of the present application. Therefore, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 15 and 30-35 be withdrawn.

Further with regard to claims 9, 10, 14, 15, 20-24 and 33-35, the Examiner alleges that it would have been *prima facie* obvious for one skilled in the art to isolate the polypeptide to which the antibodies bind from the human brain, sequence the polypeptide, and produce a nucleic acid probe comprising a polynucleotide sequence encoding the polypeptide and screen a human brain cDNA library to identify a clone comprising a cDNA encoding the polypeptide to which the anti-CV2 antibodies bind, because, essentially it would be important to understand the pathology associated with

anti-CV2 antibodies (i.e., the motivation existed) and because conventional and routine methods could be employed (i.e., there was a reasonable expectation of success).

Applicants respectfully submit that the alleged combination of art does not establish a *prima facie* case of obviousness. All of the present claims recite SEQ ID No. 8. There is no teaching or suggestion in the cited art of the specific sequence or structure of the polypeptide (SEQ ID No. 8). The existence of general methods to isolate, clone and sequence nucleotides and polypeptides do not make obvious a structurally defined molecule with a specific sequence identifier as claimed in this invention. What is claimed are not methods to isolate the protein comprising SEQ ID No. 8, but the protein itself, and diagnostic methods of using the protein.

Moreover, Applicants submit that the Examiner is incorrectly applying an "obvious to try" standard as the standard for obviousness. Where the existence of a 66 kDa protein that reacts with anti-CV2 antibodies was known, it was obvious to try to obtain the specific structure of the polypeptide molecule related to that 66 kDa protein. However, although it may be obvious to try to obtain the structure, by no means is the existence of SEQ ID No. 8 obvious. (See, e.g., In re Bell, In re Baird and In re Deuel.)

Based on the foregoing discussion, Applicants respectfully submit that claims 9, 10, 14, 15, 20-22, 24 and 33-35 are not obvious from the Examiner's cited art.

In view of the foregoing, Applicants respectfully submit that the present application is in condition for allowance.

END REMARKS

(See also Attachments (1) and (2) to these Remarks attached hereto)

ATTACHMENT (1) TO ATTACHMENT A

ATTACHMENT (2) TO ATTACHMENT A

ATTACHMENT B
Amendments to the Specification

Please replace the paragraph at page 18, lines 20-22 with the following amended paragraph:

- Figure 12 represents the nucleotide sequence of ULIP-4 in man (SEQ ID No. 7), as well as SEQ ID No. 9 and SEQ ID No. 10 which provide for the inferred amino acid sequence (SEQ ID No. 8).

Please replace the paragraph at page 18, lines 31-35 (previously amended on March 25, 2002) with the following amended paragraph:

The amino acid sequence has been completed in SEQ ID No. 8 by 19 C-terminal amino acids (No. 554 to No. ~~568~~572). This C-terminal region which is missing in Figure 12 is very well conserved between rat and mice ULIP-4 as well as between the different ULIPs. SEQ ID No. 8 is further divided into SEQ ID Nos. 9 and 10 which correspond to amino acids 1 to 55 and 57 to 553, respectively. SEQ ID No. 8 is split into two parts since position 56 of Figure 12 corresponds to an internal stop.

Please replace the Sequence Listing found in the specification on pages 45-59 (previously amended on March 25, 2002) with the substitute Sequence Listing provided herewith. A Statement Under 37 CFR § 1.821 and computer readable form of the sequence listing is also provided herewith.

ATTACHMENT C
Amendments to the Claims

Please cancel claims 23, 26 and 28 without prejudice or disclaimer.

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Previously Presented) A purified ULIP polypeptide comprising the amino acid sequence of SEQ ID No. 8.

2. (Canceled)

3. (Currently amended) An isolated ~~nucleotide~~ nucleic acid comprising a cDNA sequence coding for a ULIP polypeptide of amino acid sequence SEQ ID No. 8.

4. (Currently amended) The isolated nucleic acid according to Claim 3, comprising the sequence of SEQ ID No. 7~~, coding the ULIP polypeptide of amino acid sequence SEQ ID No. 8~~.

5. (Canceled)

6. (Previously Presented) A cloning and/or expression vector containing a nucleic acid sequence according to Claim 3.

7. (Previously Presented) A host cell transfected by a vector according to Claim 6.

8. (Canceled)

9. (Currently Amended) A composition useful for the diagnosis of paraneoplastic neurological syndromes and~~/or~~ for the early diagnosis of the formation of tumors in which anti-CV2 antibodies are expressed, said composition comprising a purified polypeptide comprising amino acid sequence SEQ ID No. 8.

10. (Currently Amended) A method for ~~using purified ULIP polypeptide comprising SEQ ID No. 8, a derivative or biologically active polypeptide fragment thereof, or of a nucleic acid comprising the nucleotide sequence of SEQ ID No. 7 for~~ detecting the presence of anti-CV2 antibodies in a biological sample, comprising:

- contacting a biological sample with a purified ULIP polypeptide comprising SEQ ID No. 8, a derivative thereof or a fragment thereof that binds to anti-CV2 antibodies, or with a polypeptide encoded by a nucleic acid comprising the nucleotide sequence of SEQ ID No. 7; and

- detecting specific immunological complexes optionally formed, the specific immunological complexes being indicative of the presence of anti-CV2 antibodies.

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Currently Amended) A method for the diagnosis of paraneoplastic neurological syndromes and~~/or~~ for the early diagnosis of the formation of tumors in which anti-CV2 antibodies are expressed, comprising:

- contacting a ~~blood~~ sample taken from an individual with a purified ULIP polypeptide, comprising SEQ ID No. 8, a derivative ~~or biologically active polypeptide fragment~~ thereof, optionally attached to a support under conditions allowing the formation of specific immunological complexes between the polypeptide and the auto-antibodies optionally present in the blood sample, and

- detecting specific immunological complexes optionally formed, the specific immunological complexes being indicative of a paraneoplastic neurological syndrome or of a tumor.

15. (Currently Amended) A kit for diagnosis in paraneoplastic neurological syndromes and for deleting early diagnosis of the formation of tumors in which anti-CV2 antibodies are expressed from a biological sample, comprising:

- at least one purified ULIP polypeptide comprising SEQ ID No. 8, a derivative ~~or biologically active polypeptide fragment~~ of the ULIP optionally attached to a support, and

- means of visualization of the formation of specific antigen/antibody complexes between an anti-POP-66 auto-antibody and the purified ULIP polypeptide, derivative or polypeptide fragment and/or means of qualification of these complexes.

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. (Canceled)

20. (Currently Amended) A method of diagnosing a paraneoplastic syndrome in a subject, said method comprising the steps of:

- contacting a sample from the subject with a polypeptide comprising a purified ULIP polypeptide selected from the group consisting of amino acid SEQ ID No. 8, a derivative or biological active polypeptide fragment thereof, said contacting carried out under conditions sufficient to allow the formation of specific immunological complexes between the peptide and antibodies present within the sample; and

- detecting the specific immunological complexes formed;

wherein the presence of immunological complexes is indicative of a paraneoplastic syndrome in said subject.

21. (Currently Amended) The method of claim 20, wherein the polypeptide ~~sequence~~ is SEQ ID No. 8.

22. (Previously Presented) The method of claim 20, wherein the polypeptide is an antigenic fragment of a polypeptide comprising amino acid sequence SEQ ID No. 8.

23. (Canceled)

24. (Currently Amended) A method of diagnosing a paraneoplastic syndrome in a subject, said method comprising the steps of:

- contacting a sample from said subject with a peptide capable of forming a specific immunological complex with an antibody, said antibody capable of forming a specific immunological complex with a polypeptide comprising amino acid sequence SEQ ID No. 8, wherein said contacting is carried out under conditions sufficient to allow the formation of specific immunological complexes between the peptide and antibodies present within the sample; and

- detecting the specific immunological complexes formed between the peptide and antibodies in the sample;

wherein the presence of ~~specific~~ immunological complexes formed between the peptide and antibodies is indicative of a paraneoplastic syndrome in said subject.

25. (Currently Amended) A method of diagnosing the formation of a tumor ~~of cancerous origin in a subject~~ that elicits an auto-immune response in a subject that results in the subject expressing anti-CV2 antibodies, said method comprising the steps of:

- contacting a sample from said subject with a polypeptide comprising amino acid sequence SEQ ID No. 8, said contacting carried out under conditions sufficient to allow the formation of specific immunological complexes between the peptide and antibodies present within the sample; and

- detecting the specific immunological complexes formed;

wherein the presence of immunological complexes is indicative of the formation of a tumor in said subject.

26. (Canceled)

27. (Previously Presented) The method of claim 25, wherein the polypeptide is an antigenic fragment of a polypeptide comprising amino acid sequence SEQ ID No. 8.

28. (Canceled)

29. (Currently Amended) A method of diagnosing the formation of a tumor ~~of cancerous origin in a subject~~ that elicits an auto-immune response in a subject that results in the subject expressing anti-CV2 antibodies, said method comprising the steps of:

- contacting a sample from said subject with a peptide capable of forming a specific immunological complex with an antibody, said antibody capable of forming a specific immunological complex with a polypeptide comprising amino acid sequence SEQ ID No. 8, wherein said contacting is carried out under conditions sufficient to allow the formation of specific immunological complexes between the peptide and antibodies present within the sample; and

detecting the specific immunological complexes formed between the peptide and antibodies in the sample;

wherein the presence of specific immunological complexes formed between the peptide and antibodies is indicative of the formation of a tumor in said subject.

30. (Previously Presented) A reagent for *ex vivo* identifying antibodies to a polypeptide according to claim 1 in a subject, said reagent comprising:

a solid support; and

a peptide comprising an antigenic portion of said polypeptide.

31. (Previously Presented) The reagent of claim 30, wherein the support comprises animal brain, and wherein the antigenic portion of the polypeptide is endogenous to said brain.

32. (Previously Presented) The reagent of claim 30, wherein the antigenic portion of a polypeptide comprising amino acid sequence of SEQ ID No. 8 is attached to said support.

33. (Previously Presented) A diagnostic kit for identifying antibodies to a polypeptide comprising amino acid sequence of SEQ ID No. 8 in a subject, said kit comprising an antigenic portion of said polypeptide or a derivative thereof.

34. (Previously Presented) The kit of claim 33, wherein the kit further comprises means of visualizing formation of said polypeptide-antibody complexes.

35. (Previously Presented) The kit of claim 33, wherein the antigenic portion of said polypeptide is purified.